REMARKS

Claims 89, 90, 92, 95-101, 103 and 106-117 are pending. Claims 111-113 and 115-117 were previously withdrawn. Claims 89, 90, 92, 95-101, 103, 106-110 and 114 are under examination. Claims 110, 113 and 114 are canceled without prejudice to Applicant's right to pursue these claims in a related application. Claims 89, 92, 95, 96, 98, 99, 103, 106, 107 and 109 have been amended. Support for the amendments can found throughout the specification and the claims as filed. In particular, support for the amendments to claims 89 and 99 can be found on page 40, line 21 to page 42, line 3; page 8, lines 9-30; page 11, lines 22-28; and in originally filed claim 31. Support for the amendments to claims 92, 96, 98, 103, 107 and 109 can be found on page 40, line 21 to page 42, line 3; page 11, lines 22-28; and in originally filed claim 31. Support for the amendments to claims 95 and 96 can be found on page 10, line 22 to page 11, line 9. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Interview Summary

Applicant would like to thank Examiner Sang for the courtesy of conducting the telephone interview of June 9, 2010 regarding the above-identified application. It is believed that the amendments above and the remarks below substantially conform to the subject matter discussed in the interview. Reconsideration of the following rejection is respectfully requested.

Rejection Under 35 USC § 103(a)

The rejection of claims 89, 90, 92, 95-101, 103, 106-110 and 114 under 35 USC § 103(a), as being obvious over Froesch et al., Proceeding of the American Association for Cancer Research, Annual Meeting, 89:13 (March 1998), in view of Tang et al., Journal of Clinical Oncology, 17(6):1710-1719 (1999); Yawata et al., Oncogene, 16:2681-2686 (1998); and Sano et al. (U.S. Patent No. 5,665,539), is respectfully traversed. The Office asserts that Froesch et al. allegedly disclose BAG-1 protein (cytosolic BAG protein) is expressed in all 9/9 prostate cancer cell lines and 51/51 archival prostate tumor specimens (see Abstract). The Office further asserts that the expression of cytosolic BAG-1 protein in prostate cancer was known, as evidenced by the disclosure of Takayama et al., Cancer Res. 58:3116-3131 (1998). The Office asserts that

Tang et al. allegedly disclose that BAG-1 is overexpressed in the majority of invasive breast carcinomas, and by multivariate analysis, BAG-1 expression was significantly associated with shorter disease-free and overall survival (Abstract and Figures 3 and 4). The Office asserts that Yawata et al. allegedly disclose that overproduction of BAG-1 enhances cancer cell metastasis. The Office asserts that one would have been motivated to determine the prognostic function of both cytosolic and nuclear BAG-1 protein in prostate cancer based on the disclosure of Froesch et al., Tang et al. and Yawata et al. Furthermore, one of ordinary skill in the art would have allegedly had a reasonable expectation of success because Froesch et al. allegedly detected BAG-1 protein in all 9/9 prostate cancer cell lines and all 51/51 prostate tumor specimens, Tang et al. allegedly showed that in multivariate analysis, BAG-1 expression was significantly associated with shorter disease-free and overall survival, and Yawata et al. allegedly showed that overexpression of BAG-1 increased the metastatic potential of tumor cells *in vivo*. Applicant respectfully maintains the position of record and submits that the claimed methods are unobvious over Froesch et al., alone or in combination with Tang et al., Yawata et al., and/or Sano et al.

Applicant submits that (1) the Office does not articulate the rationale underlying the instant rejection as required by the U.S. Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.* 550 U.S. 398; 127 S. Ct. 1727; 167 L. Ed. 2d 705, 82 USPQ2d 1385, 1395 (2007) and articulated in the Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 (see MPEP §2141); and (2) that there was no reasonable expectation of success when combining the cited references.

The U.S. Patent and Trademark Office recently promulgated guidelines for Examiners in making obviousness determinations in view of the U.S. Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.* (see MPEP §2141). One important feature of the guidelines is an *explicit requirement* that an Examiner provide articulated reasons for the factual determinations underlying an asserted *prima facie* case of obviousness. This focus is consistent with the rule set down in the *KSR* decision that a factfinder must provide "reasons" why an invention would have been obvious to one of ordinary skill in the art." *KSR* at 1741. In explicating this aspect of the Supreme Court's decision, the guidelines set forth several different rationales that can be used to support an obvious rejection (see MPEP §2143). The guidelines further set forth explicit factual findings that an Examiner must articulate to support an obviousness rejection under each

rationale. In the present case the Examiner has applied the "teaching, suggestion or motivation" test, identified in the guidelines as rationale (G). For an obviousness rejection based on this rationale for combining references, the Examiner *is required to articulate* the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine reference teachings; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. While it is proper for the motivation to combine to be implicit and be found in the knowledge of one of ordinary skill in the art, or, in some cases, the nature of the problem to be solved (*KSR Int'l Co. v. Teleflex Inc.*), the Examiner has not articulated where such motivation is found other than asserting aspects of the references, and in some cases mischaracterizing the references, as discussed below. Furthermore, the present Office Action fails to articulate a finding that there would have been a reasonable expectation of success when combining the cited references (see discussion below).

Presently, claim 89, and all dependent claims thereof, are directed towards a method for determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer by determining a cytosolic BAG-1 protein level in a cancerous prostate tissue sample from the patient and comparing the cytosolic BAG-1 protein level in the sample to a reference cytosolic BAG-1 protein level, the reference cytosolic BAG-1 protein level being a level of cytosolic BAG-1 protein above which correlates with an increased risk of tumor recurrence or spread and below which correlates with a decreased risk of tumor recurrence or spread, thereby determining the risk of tumor recurrence or spread in the patient. Presently, claim 99, and all dependent claims thereof, are directed towards a method for determining a prognosis of survival in a patient suffering from prostate cancer by determining a cytosolic BAG-1 protein level in a cancerous prostate tissue sample from the patient and comparing the cytosolic BAG-1 protein level in the sample to a reference cytosolic BAG-1 protein level, the reference cytosolic BAG-1 protein level being a level of cytosolic BAG-1 protein above which correlates with decreased survival and below which correlates with increased survival, thereby determining a prognosis of survival in the patient.

As discussed with Examiner Sang in the telephonic interview, Applicant respectfully submits that one of ordinary skill in the art would have no motivation to combine the disclosure of Froesch et al. with the disclosures of Tang et al. and/or Yawata et al. to arrive at the claimed methods. At best, Froesch et al. disclose the expression of BAG-1L in prostate cancer (see Title and last sentence of abstract). At best, Tang et al. disclose that breast cancer patients whose tumors expressed nuclear BAG-1 tended to have shorter disease-free and overall survival (see page 1716, first column, lines 3-6, and Figure 4). At best, Yawata et al. disclose that overexpression of Bcl-2 or BAG-1 enhances peritoneal dissemination of human gastric MKN74 cells in nude mice (see Yawata at page 2682, left column, paragraph 1, lines 3-5; and page 2684 under the heading of *peritoneal dissemination of MKN74 transfectants*). One of skill in the art would have no motivation to combine the disclosure of Froesch et al. regarding prostate cancer, with the disclosure of Tang et al. regarding breast cancer and the disclosure of Yawata et al. regarding gastric cancer, to achieve the claimed methods. Applicants submit that a person having ordinary skill in the art and having the capability of appreciating the complexity of scientific issues in cancer, would most likely not combine the disclosures of such divergent cancer types to arrive at a method for determining the risk of tumor recurrence or spread in patients suffering from prostate cancer or determining a prognosis of survival of a prostate cancer patient, as claimed.

Furthermore, as discussed with Examiner Sang, assuming, *arguendo*, that the references were combined, there would be no expectation of success because the disclosures of Froesch et al. and Tang et al. as evidenced by Takayama et al., when viewed as a whole, would lead one of ordinary skill in the art to conclude that the nuclear isoform of BAG-1, i.e. BAG-1L, is involved in development of prostate cancer. Thus, the cited references are teaching away from the claimed cytosolic BAG-1 isoform.

With regard to Froesch et al., the Office asserts that the BAG-1 protein (cytosolic BAG protein) is expressed in all 9/9 prostate cancer cell lines and 51/51 archival prostate tumor specimens. Applicant maintains that, at best, the disclosure of Froesch et al. is directed towards BAG-1L expression in prostate cancer. Specifically, the title recites "BAG-1L protein is expressed in prostate cancers and enhances androgen receptor function." (emphasis added). Furthermore, the abstract discloses that BAG-1L, not BAG-1 [cytosolic BAG-1], co-

immunopreciptated with androgen receptors (AR) from LNCaP cell lysates and markedly enhanced the ability of androgen receptors to trans-activate reporter gene plasmids in PC3 and other cell lines. The abstract concludes by reciting "These findings implicate BAG-1L as a novel regulator of AR function in prostate cancers." (emphasis added). BAG-1L is the longer protein isoform of the BAG-1 gene, as described in the specification on page 10, line 22 to page 11, line 9 and is known to one of skill in the art to be the isoform which contains a nuclear localization signal in the N-terminal region of the protein (see Takayama et al. page 3121, Figure 3C). BAG-1L is described in the specification to be the isoform found in the nuclear portion of the cell (see page 40, lines 7-11). Thus, the disclosure of Froesch et al. would, at most, lead one of ordinary skill in the art towards the BAG-1L isoform, not the claimed cytosolic BAG-1 protein. Accordingly, Applicant submits that Froesch et al. teach away from the claimed cytosolic BAG-1 isoform.

With regard to Tang et al., the Office asserts that Tang et al. allegedly showed by multivariate analysis that BAG-1 expression was significantly associated with shorter disease-free and overall survival (Abstract and Figures 3 and 4). Applicant respectfully disagrees with the characterization of Tang et al. and submits that the Office is mischaracterizing the disclosure of Tang et al. Although Tang et al. may disclose that BAG-1 expression was significantly associated with shorter disease-free and overall survival using one type of analysis, when the disclosure of Tang et al. is taken as a whole, one of ordinary skill would most likely conclude there is little, if any, evidence that the expression pattern of BAG-1 is associated with survival. Furthermore, if anything can be gleaned from the disclosure of Tang et al., it is that only the nuclear expression of BAG-1, i.e. BAG-1L, might be correlated with survival. Applicant directs the Office to page 1713, first column last sentence, which characterizes the results of the multivariate analysis as follows:

> However, BAG-1 expression ($P = .0052$ and $P = .0033$) and stage ($P = .0000$ and $P = .0001$) were significantly correlated with shorter disease-free and overall survival in the multivariate analysis, as listed in Table 3. (emphasis added)

Tang et al. disclose the following in Table 3 found on page 1714, second column:

Table 3. Survival Analysis by Multivariate Cox Regression

Factor	Disease-Free Survival (*P*)	Overall Survival (*P*)
Age	.0800	.0925
Differentiation	.0070*	.3334
BAG-1 expression	.0052*	.0033*
BAG-1 pattern	.8544	.7199
Stage	.0000*	.0001*
Tumor type	.9914	.9986

* $P < .01$

Thus, Tang et al. disclose that expression of BAG-1 and the stage of cancer were statistically correlated with shorter disease-free and overall survival using the multivariate analysis, whereas the BAG-1 pattern, i.e. the nuclear and cytoplasmic expression pattern, was not statistically correlated with disease-free and overall survival ($P = .8544$ and $P = .7199$, respectively). Tang et al. also disclose that when analyzed by univariate analysis, BAG-1 expression pattern did not correlate with either disease-free or overall survival (page 1713, first column, lines 5-6 from bottom). At best, Tang et al. disclose that a Kaplan-Meier survival analysis showed that nuclear expression of BAG-1 only tended to be associated with a shorter disease free and overall survival, but the differences did not reach statistical significance (see page 1716, first column, lines 3-6, and Figure 4). Accordingly, Applicant submits that Tang et al. teach away from the claimed cytosolic BAG-1 isoform.

Regarding the disclosure of Takayama et al., the Office asserts that the expression of cytosolic BAG-1 protein in prostate cancer was known, as evidenced by the disclosure of Takayama et al. Applicant respectfully disagrees with the characterization of Takayama et al. Although Takayama et al. may disclose that seven prostate cancer cell lines express BAG-1, when the disclosure of Takayama et al. is taken as a whole, one of ordinary skill would most likely consider that the expression of BAG-1L is associated with the development of cancer. Applicant respectfully directs the Office to page 3130, right column, lines 8-22, wherein Takayama et al. characterize their results from Table 2:

> In contrast, the BAG-1L protein was more variable in its expression, and in a few instances BAG-1L levels approached or

> were equivalent to the levels of ~36-kDa BAG-1 in tumor lines such as the breast cancer BT-549, the prostate cancer lines DU-145 and LN-CaP, and the leukemia line Jurkat. Indeed, breast cancer, prostate cancer, and leukemia cell lines were the most consistent expressors of the BAG-1L protein, with seven of seven prostate, seven of eight breast and four of five leukemia cell lines containing immunodetectable levels of this protein. An intriguing possibility is that BAG-1L, with its proclivity for nuclear targeting, may contribute to the regulation of nuclear hormone receptor function in these types of tumors, given the prominent role played by androgen receptor, ER, and glucocorticoid receptor in cancer of the prostate, breast and lymphoid organs, respectively. (emphasis added)

Takayama et al. also summarize in the last sentence of the abstract:

> In contrast to normal tissues, which only rarely expressed BAG-1L, tumor cell lines commonly contained BAG-1L protein, including most prostate, breast, and leukemia cell lines, suggesting that a change in BAG-1 mRNA translation frequently accompanies malignant transformation. (emphasis added)

Thus, Takayama et al. disclose that the expression of the nuclear BAG-1L isoform accompanies malignant transformation. Accordingly, Applicant submits that Takayama et al. teach away from the claimed cytosolic BAG-1 isoform.

Regarding the disclosure of Sano et al., Applicant maintains that, at best, the reference discloses an immuno-PCR method. Thus, the disclosure of Sano et al. does not provide any reasonable expectation of success for one of skill in the art to practice the claimed methods, when combined with the disclosures of Froesch et al. and/or Tang et al. and/or Yawata et al.

In conclusion, given that the Office has not provided an articulated reason for combining disclosures related to such disparate cancer types and, even if combined, the cited references do not provide a reasonable expectation of success in practicing a method wherein cytosolic BAG-1 protein levels are used to determine the risk of tumor recurrence or spread in a patient suffering from prostate cancer and a prognosis of survival for a patient suffering from prostate cancer, Applicant respectfully submits that Froesch et al., alone or in combination, with Tang et al. and/or Yawata et al. and/or Sano et al., does not teach or suggest the claimed methods. Absent such a teaching or suggestion, Applicant respectfully submits that the claimed methods are

unobvious over Froesch et al., alone or in combination with Tang et al., Yawata et al., and/or Sano et al. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

Applicant submits that this Response to Final Rejection at least places this application in better form for appeal. This Amendment is necessary as it clarifies and/or narrows the issues for consideration by the Board and was not earlier presented because Applicant believed that the prior responses placed this application in condition for allowance, for at least the reasons set forth in those responses. Accordingly, entry of the present amendments, as an earnest attempt to advance prosecution and/or to reduce the number of issues, is requested under 37 C.F.R. §1.116.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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